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Published in:
Kidney International

DOI:
[10.1038/ki.2013.553](https://doi.org/10.1038/ki.2013.553)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Wen, C. P., Matsushita, K., Coresh, J., Iseki, K., Islam, M., Katz, R., McClellan, W., Peralta, C. A., Wang, H., de Zeeuw, D., Astor, B. C., Gansevoort, R. T., Levey, A. S., Levin, A., & Chronic Kidney Dis Prognosis (2014). Relative risks of chronic kidney disease for mortality and end-stage renal disease across races are similar. *Kidney International*, 86(4), 819-827. <https://doi.org/10.1038/ki.2013.553>

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Relative risks of chronic kidney disease for mortality and end-stage renal disease across races are similar

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Some suggest race-specific cutpoints for kidney measures to define and stage chronic kidney disease (CKD), but evidence for race-specific clinical impact is limited. To address this issue, we compared hazard ratios of estimated glomerular filtration rates (eGFR) and albuminuria across races using meta-regression in 1.1 million adults (75% Asians, 21% Whites, and 4% Blacks) from 45 cohorts. Results came mainly from 25 general population cohorts comprising 0.9 million individuals. The associations of lower eGFR and higher albuminuria with mortality and end-stage renal disease (ESRD) were largely similar across races. For example, in Asians, Whites, and Blacks, the adjusted hazard ratios (95% confidence interval) for eGFR 45–59 versus 90–104 ml/min per 1.73 m² were 1.3 (1.2–1.3), 1.1 (1.0–1.2), and 1.3 (1.1–1.7) for all-cause mortality, 1.6 (1.5–1.7), 1.4 (1.2–1.7), and 1.4 (0.7–2.9) for cardiovascular mortality, and 27.6 (11.1–68.7), 11.2 (6.0–20.9), and 4.1 (2.2–7.5) for ESRD, respectively. The corresponding hazard ratios for urine albumin-to-creatinine ratio 30–299 mg/g or dipstick 1+ versus an albumin-to-creatinine ratio under 10 or dipstick negative were 1.6 (1.4–1.8), 1.7 (1.5–1.9), and 1.8 (1.7–2.1) for all-cause mortality, 1.7 (1.4–2.0), 1.8 (1.5–2.1), and 2.8 (2.2–3.6) for cardiovascular mortality, and 7.4 (2.0–27.6), 4.0 (2.8–5.9), and 5.6 (3.4–9.2) for ESRD, respectively. Thus, the relative mortality or ESRD risks of lower eGFR and higher albuminuria were largely similar

among three major races, supporting similar clinical approach to CKD definition and staging, across races.

Kidney International (2014) **86**, 819–827; doi:10.1038/ki.2013.553;

published online 12 February 2014

KEYWORDS: chronic kidney disease; end-stage renal disease; epidemiology and outcomes; ethnicity; mortality risk

Chronic kidney disease (CKD) is a global public health problem,^{1–3} affecting 10–16% of the adult population in several continents^{4–7} and increasing the risk of adverse outcomes.^{8–12} The definition and staging of CKD is based on the level of glomerular filtration rate (GFR) and the presence of kidney damage, usually ascertained as albuminuria.^{1,11,13} However, the comparability of GFR and albuminuria measures across racial groups and their relationship with risk have not been fully explored,¹⁴ although some have suggested race-specific thresholds for GFR and albuminuria to define and stage CKD.¹⁵ The primary objective of this study was to quantify the associations of GFR and albuminuria with risk for all-cause and cardiovascular mortality, and end-stage renal disease (ESRD) among Asians, Whites, and Blacks, three major races in the world, and assess whether there are any substantial differences across the races.

RESULTS

Study populations

A total of 1,130,472 individuals were studied, including 75% Asians (mostly Eastern Asians), 21% Whites, and 4% Blacks. Majority of the study population, 83% or 940,366

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Received 31 July 2013; revised 23 October 2013; accepted 21 November 2013; published online 12 February 2014

individuals, were from 25 general population cohorts, with the remaining 13% or 151,494 individuals from 7 high-risk cohorts, and 3% or 38,612 individuals from 13 CKD cohorts (Table 1). Thus, our primary analyses were conducted in the general population cohorts, and results for the high-risk cohorts and CKD cohorts were shown in Supplementary Materials separately. Asians comprised the majority of the general population cohorts (87%), but not the high-risk (6%) or CKD (12%) cohorts, and mainly came from cohorts based on data from comprehensive health screening programs for the healthy population. Accordingly, Asians tended to have a lower risk profile (younger age and lower prevalence of comorbid conditions) as compared with Whites and Blacks. Although most Asians were from Asian cohorts, most Blacks were from US cohorts. There were differences in the methods for ascertainment of albuminuria among the general population cohorts: only 1% of Asians had albumin-to-creatinine ratio (ACR) data, whereas ACR data were available in 73% of Whites and 100% of Blacks included in the meta-analysis, reflecting different medical and research settings.

Estimated glomerular filtration rate and albuminuria distributions by race

In the general population cohorts, the crude prevalence of reduced estimated glomerular filtration rate (eGFR; <60 ml/min per 1.73 m^2) in Asians, Whites, and Blacks was 5.1, 15.8, and 9.4%, respectively (Supplementary Figure S1A online). The prevalence of elevated albuminuria (≥ 30 mg/g by ACR or $\geq 1+$ by urine dipstick) in the three races was 2.8, 9.9, and 16.6%, respectively (Supplementary Figure S1B online). The difference in prevalence of reduced eGFR and elevated albuminuria across racial groups was attenuated after age standardization, particularly for reduced eGFR (Supplementary Figure S1C and D online). In the high-risk cohorts, the crude prevalence of decreased eGFR and high albuminuria were 11.6 and 24.0% in Asians, 18.7 and 20.6% in Whites, and 10.4 and 13.5% in Blacks, respectively (Supplementary Figure S2 online).

Incidence rates of mortality and ESRD by race

We observed 38,696 all-cause deaths and 9065 cardiovascular disease (CVD) deaths in Asians (mean follow-up of 9.2 years), 20,079 and 7325 cases in Whites (mean follow-up of 8.4 years), and 2485 and 436 cases in Blacks (mean follow-up of 6.6 years; Supplementary Table S1 online). Crude rates for all-cause and CVD mortality in the general population cohorts were 5.9 and 1.4 per 1000 person-years in Asians, 24.1 and 10.4 in Whites, and 18.7 and 5.5 in Blacks, respectively (Supplementary Figure S3 online). After age standardization, mortality rates were higher in Blacks compared with that in Whites, whereas the lower rates in Asians persisted. The variation in mortality rates was as great among studies within races as among races within studies. Among the studies with data on ESRD, crude incidence rates of ESRD per 1000 person-years were 0.3 in Asians, 0.8 in Whites, and 2.8 in Blacks.

Independent relationships of eGFR and albuminuria with clinical risk by race

Figure 1 shows hazard ratios (HRs) for all-cause mortality, CVD mortality, and ESRD in the general population cohorts by race for eGFR from 15 to 120 ml/min per 1.73 m^2 compared with the reference point at eGFR 95 ml/min per 1.73 m^2 . The patterns for each outcome were qualitatively similar among three races across most of the range of eGFRs, with higher risk at lower eGFR. For all-cause and CVD mortality, although there was variation across races in the eGFR thresholds below which the HRs were significantly greater than the reference point, partially owing to difference in the precision of estimates across races, the HR reached significance at eGFR between 60 and 75 ml/min per 1.73 m^2 in most analyses and did not differ significantly for a given eGFR among races, except for small ranges noted at the bottom of Figure 1. For ESRD, the threshold eGFR varied from 65 to 83 ml/min per 1.73 m^2 for all three races, although the pattern was least steep in blacks for eGFR <30 ml/min per 1.73 m^2 .

Figure 2 shows HRs for all three outcomes by races according to albuminuria categories (ACR <10 , 10–29, 30–299, and ≥ 300 mg/g or urine dipstick levels negative, trace, 1+ and $\geq 2+$, respectively; Supplementary Figure S4 online shows the association for ACR as a continuous variable). Again, the patterns for each outcome were similar among races, with higher HRs for higher albuminuria. The only significant difference was higher CVD mortality in Blacks with ACR 30–299 mg/g. In all races, the threshold category above which the HRs for mortality outcomes was significantly greater than the reference category was ACR ≥ 10 mg/g or dipstick \geq trace. Although data were limited, the independent associations of low eGFR and high albuminuria with three outcomes were largely similar across three races in both high-risk and CKD cohorts (Supplementary Figures S5–S8 online).

Combined relationships of eGFR and albuminuria with clinical risk by race

Figure 3 shows the adjusted HRs for all-cause mortality, CVD mortality, and ESRD in the general population cohorts by eGFR and albuminuria categories compared with the reference categories of eGFR 90–104 ml/min per 1.73 m^2 and ACR <10 mg/g or dipstick negative. Consistent with the results in Figures 1 and 2, all-cause mortality risks for eGFR categories and albuminuria categories (marginal rows and columns in Figure 3) were similar for Asians, Whites, and Blacks. For example, in Asians, Whites, and Blacks, compared with eGFR 90–104 ml/min per 1.73 m^2 , the HR (95% confidence interval) for eGFR 45–59 ml/min per 1.73 m^2 was 1.25 (1.20–1.31), 1.09 (0.97–1.22), and 1.33 (1.07–1.65) for all-cause mortality, 1.59 (1.45–1.74), 1.40 (1.17–1.68), and 1.44 (0.72–2.86) for cardiovascular mortality, and 27.6 (11.1–68.7), 11.2 (6.01–20.9), and 4.05 (2.18–7.51) for ESRD, respectively. The corresponding HRs for ACR 30–299 mg/g or dipstick 1+ compared with ACR <10 mg/g or dipstick negative were 1.61 (1.41–1.84), 1.68 (1.50–1.88), and 1.84 (1.65–2.06) for all-cause mortality, 1.66 (1.37–2.01), 1.76 (1.49–2.09), and

Table 1 | Characteristics of individual studies by race (Asians, Whites, and Blacks)

[illegible]

cardiovascular disease; PCR, urine protein-to-creatinine ratio; NA, not available.

Proportion of participants with ACR ≥ 30 mg/g or PCR ≥ 30 mg/g or alipstick protein ≥ 1 .

Not included in meta-analysis owing to small number of events (<10) in this racial group studies with ACh.

Studies with PCR

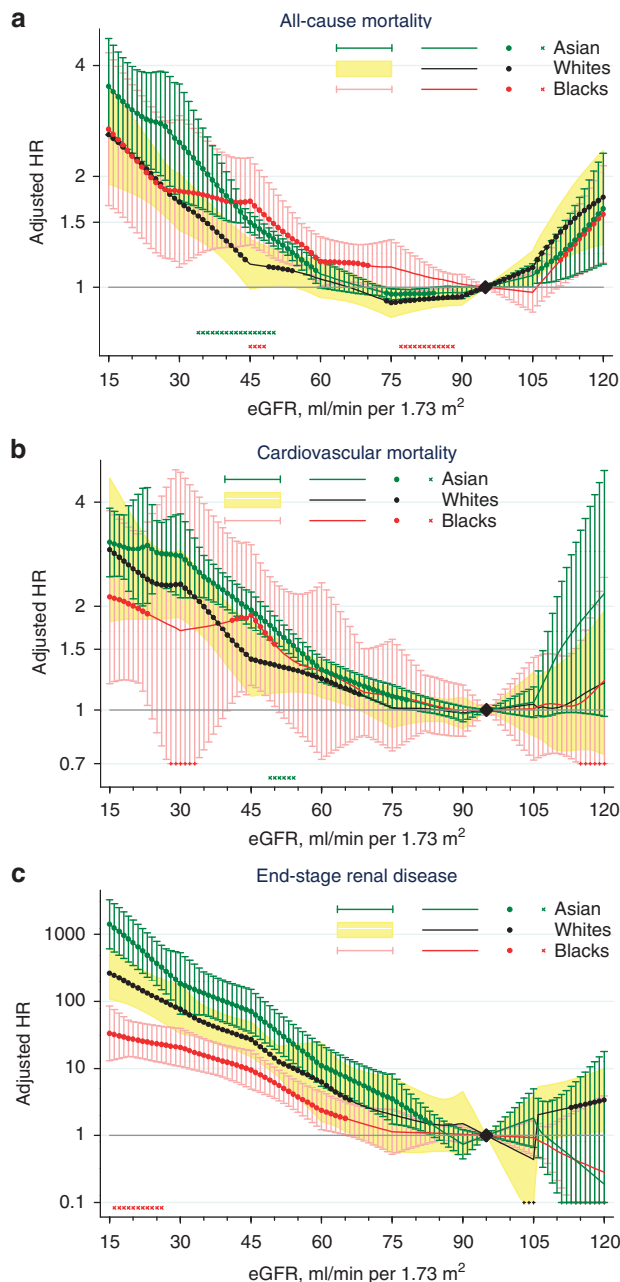


Figure 1 | Association of estimated glomerular filtration rate (eGFR) with all-cause mortality (a), cardiovascular mortality (b), and end-stage renal disease (ESRD) (c) across three racial groups in general population cohorts. The shaded area or whiskers represent 95% confidence intervals (95% CIs). The reference (diamond) is eGFR 95 ml/min per 1.73 m². Dots represent statistically significant points. Difference in hazard ratios (HRs) among racial groups were tested using meta-regression with Whites as a reference, and stars along the bottom of each panel indicate a significant interaction at $P < 0.05$. HRs were adjusted for age, sex, smoking, systolic blood pressure, history of cardiovascular disease, diabetes, serum total cholesterol concentration, body mass index, and albuminuria.

2.79 (2.15–3.62) for CVD mortality, and 7.39 (1.98–27.6), 4.04 (2.75–5.94), and 5.55 (3.36–9.18) for ESRD, respectively. The HRs were quantitatively consistent across most of the studies for three outcomes (Supplementary Figures S9–S11 online).

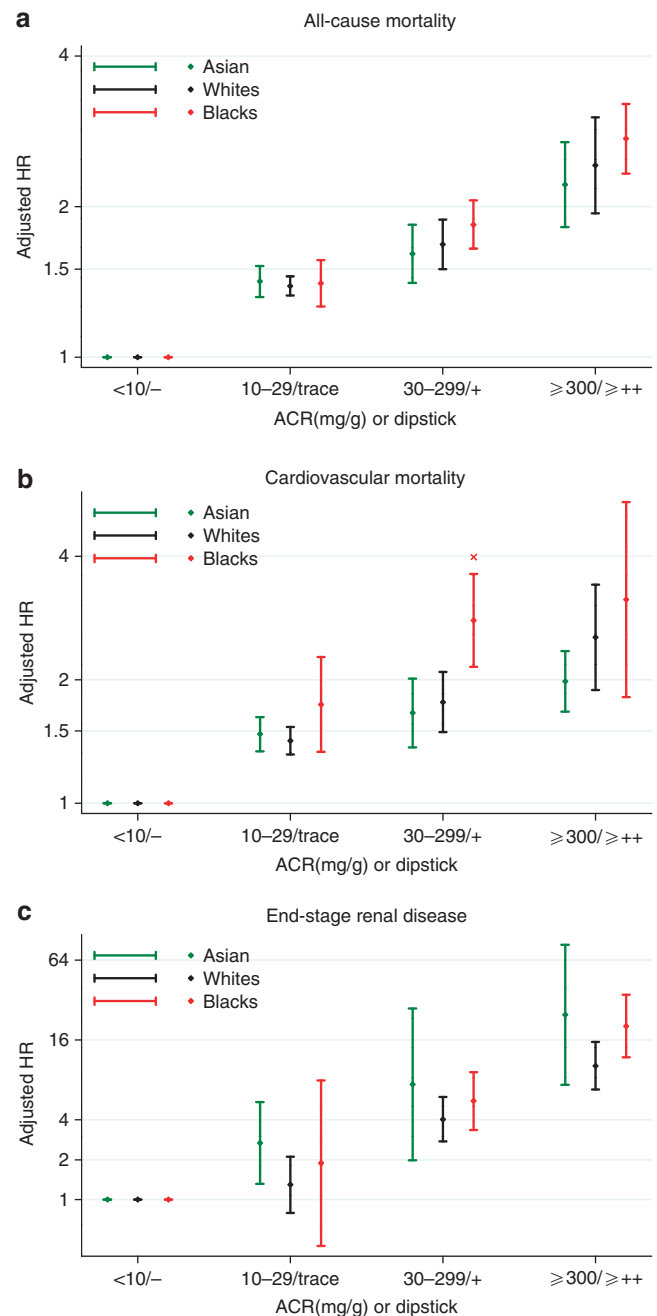


Figure 2 | Association of albuminuria with all-cause mortality (a), cardiovascular mortality (b), and end-stage renal disease (ESRD) (c) across three racial groups in general population cohorts. The whiskers represent 95% confidence intervals (95% CIs). The reference category is urine albumin-to-creatinine ratio (ACR) <10 mg/g or dipstick negative. Dots represent statistically significant points. Differences in hazard ratios (HRs) among racial groups were tested using meta-regression with Whites as a reference. HRs were adjusted for age, sex, smoking, systolic blood pressure, history of cardiovascular disease, diabetes, serum total cholesterol concentration, body mass index, and estimated glomerular filtration rate (eGFR) categories.

The pattern for categories based on eGFR and albuminuria (cells in Figure 3) was also qualitatively similar among the three races, showing a multiplicatively higher risk for lower eGFR and higher albuminuria, with limited interactions.

eGFR	Asian						White						Black					
	ACR/Dipstick						ACR/Dipstick						ACR/Dipstick					
	<10 / Dip "+"	10-29 / Dip "+"	30+ / Dip "+"	300+ / Dip "≥2"			<10 / Dip "+"	10-29 / Dip "+"	30+ / Dip "+"	300+ / Dip "≥2"			<10 / Dip "+"	10-29 / Dip "+"	30+ / Dip "+"	300+ / Dip "≥2"		
All-cause mortality																		
≥105	1.14 (1.00, 1.30)	1.67 (1.35, 2.07)	3.59 (2.18, 5.91)	5.41 (3.25, 9.01)	1.17 (1.03, 8.84)		1.23 (1.00, 1.51)	1.95 (1.49, 2.56)	2.88 (2.00, 4.15)	7.63 (4.11, 14.1)	1.26 (1.08, 1.47)		1.40 (1.08, 1.83)	1.57 (1.23, 2.02)	2.07 (1.58, 2.70)	3.64 (2.26, 5.86)	1.20 (1.05, 1.38)	
90-104	REF	1.58 (1.41, 1.77)	1.79 (1.45, 2.21)	3.42 (2.05, 5.68)			REF	1.55 (1.33, 1.79)	1.74 (1.51, 2.00)	3.67 (2.35, 5.71)			REF	1.43 (1.14, 1.79)	1.94 (1.52, 2.47)	3.65 (2.52, 5.36)		
75-89	0.95 (0.89, 1.01)	1.27 (1.07, 1.50)	1.60 (1.21, 2.11)	2.54 (1.66, 3.89)	0.94 (0.88, 1.00)		0.91 (0.81, 1.01)	1.37 (1.25, 1.50)	1.61 (1.38, 1.89)	2.07 (1.59, 2.68)	0.90 (0.84, 0.97)		1.11 (0.93, 1.32)	1.45 (1.14, 1.83)	2.11 (1.65, 2.70)	3.22 (2.14, 4.87)	1.04 (0.90, 1.22)	
60-74	1.02 (0.95, 1.09)	1.30 (1.20, 1.41)	1.71 (1.50, 1.95)	2.10 (1.67, 2.64)	1.00 (0.94, 1.07)		0.99 (0.88, 1.12)	1.46 (1.32, 1.63)	1.78 (1.50, 2.12)	2.49 (1.77, 3.51)	0.99 (0.90, 1.08)		1.15 (0.94, 1.39)	1.76 (1.40, 2.21)	2.27 (1.67, 3.10)	3.41 (2.43, 4.79)	1.16 (1.02, 1.32)	
45-59	1.28 (1.23, 1.35)	1.95 (1.76, 2.16)	1.84 (1.51, 2.25)	2.76 (2.47, 3.08)	1.25 (1.20, 1.31)		1.09 (0.91, 1.31)	1.64 (1.40, 1.92)	1.94 (1.50, 2.50)	2.92 (2.05, 4.15)	1.09 (0.97, 1.22)		1.28 (1.00, 1.63)	2.40 (1.84, 3.13)	2.47 (1.65, 3.69)	4.27 (2.86, 6.38)	1.33 (1.07, 1.65)	
30-44	1.88 (1.60, 2.21)	2.97 (1.15, 7.65)	2.73 (2.34, 3.20)	3.63 (3.01, 4.38)	1.73 (1.53, 1.97)		1.51 (1.20, 1.90)	2.23 (1.85, 2.69)	2.58 (1.90, 3.51)	3.85 (2.59, 5.73)	1.43 (1.26, 1.63)		2.32 (1.40, 3.84)	2.04 (0.81, 5.12)	4.27 (3.22, 5.67)	5.88 (3.10, 11.1)	1.99 (1.47, 2.69)	
15-29	3.35 (2.14, 5.26)	4.10 (3.15, 5.33)	6.00 (2.79, 12.9)	8.94 (4.87, 16.4)	3.30 (2.11, 5.16)		3.22 (1.84, 5.63)	3.43 (2.09, 5.61)	2.98 (2.31, 3.87)	5.75 (3.66, 9.02)	2.08 (1.60, 2.72)		2.27 (0.49, 10.59)	5.06 (2.36, 10.86)	4.86 (2.21, 10.66)	5.33 (3.73, 7.62)	2.03 (1.42, 2.91)	
<15	8.22 (4.02, 16.8)	8.10 (5.58, 11.8)	4.67 (1.25, 17.4)	11.8 (6.51, 21.2)	4.12 (2.91, 5.82)		3.81 (1.51, 9.63)	4.43 (2.01, 9.23)	6.22 (3.77, 10.3)	9.68 (6.27, 15.0)	3.74 (2.66, 5.27)		21.3 (2.95, 154)	14.8 (6.89, 32.0)	11.7 (6.25, 22.0)	4.44 (2.23, 8.84)		
		1.42 (1.32, 1.52)	1.61 (1.41, 1.84)	2.21 (1.82, 2.69)				1.39 (1.33, 1.45)	1.68 (1.50, 1.88)	2.42 (1.94, 3.01)			1.40 (1.26, 1.56)	1.84 (1.65, 2.06)	2.73 (2.33, 3.21)			
CVD mortality																		
≥105	1.36 (0.85, 2.17)	1.72 (0.96, 3.09)	5.23 (3.01, 9.08)	8.85 (4.40, 17.8)	1.47 (0.96, 2.26)		0.98 (0.58, 1.34)	2.14 (1.19, 3.88)	4.13 (2.02, 8.46)	7.63 (2.34, 24.9)	0.95 (0.70, 1.27)		1.49 (0.62, 3.56)	1.62 (0.83, 3.15)	3.76 (1.54, 9.21)	1.59 (0.21, 12.2)	1.12 (0.78, 1.61)	
90-104	REF	1.98 (1.51, 2.59)	1.78 (1.29, 2.47)	3.33 (1.71, 6.46)			REF	1.48 (1.03, 2.14)	1.80 (1.36, 2.37)	3.11 (1.82, 5.30)			REF	2.00 (1.18, 3.40)	1.80 (0.95, 3.41)	5.76 (1.74, 26.3)		
75-89	1.08 (1.00, 1.16)	1.78 (1.45, 2.19)	1.77 (1.20, 2.61)	2.39 (1.85, 3.07)	1.06 (0.99, 1.14)		0.98 (0.84, 1.15)	1.48 (1.24, 1.78)	1.79 (1.46, 2.20)	3.06 (2.14, 4.39)	1.03 (0.92, 1.15)		1.20 (0.70, 2.05)	1.74 (0.99, 3.04)	3.83 (1.74, 8.45)	4.02 (0.55, 29.5)	1.18 (0.79, 1.77)	
60-74	1.25 (1.09, 1.42)	1.80 (1.47, 2.20)	2.50 (1.98, 3.17)	2.18 (1.71, 2.79)	1.20 (1.12, 1.29)		1.12 (0.99, 1.25)	1.67 (1.39, 1.91)	2.01 (1.64, 2.47)	3.17 (2.16, 4.66)	1.15 (1.02, 1.29)		1.16 (0.50, 2.69)	1.70 (0.97, 2.99)	3.30 (1.54, 7.06)	7.14 (1.90, 28.3)	1.13 (0.80, 1.61)	
45-59	1.71 (1.50, 1.95)	2.39 (1.91, 2.98)	2.95 (1.89, 2.94)	1.59 (1.84, 4.73)	1.59 (1.45, 1.74)		1.39 (1.04, 1.59)	1.87 (1.50, 2.33)	2.50 (1.78, 3.49)	3.76 (2.79, 5.06)	1.40 (1.17, 1.68)		1.47 (0.51, 4.21)	2.85 (1.18, 6.86)	4.66 (1.48, 14.7)	5.33 (1.53, 18.6)	1.44 (0.72, 2.86)	
30-44	2.59 (2.15, 3.13)	3.82 (2.81, 5.18)	3.68 (2.66, 5.10)	4.83 (3.74, 6.25)	2.35 (2.05, 2.68)		2.14 (1.71, 2.67)	2.46 (1.52, 3.97)	3.11 (2.28, 4.22)	1.84 (3.07, 7.51)	1.17 (1.57, 2.15)		4.49 (1.17, 17.2)	3.10 (0.56, 17.1)	8.35 (2.77, 25.2)	14.41 (1.41, 50.9)	1.12 (1.12, 54.5)	
15-29	4.71 (2.27, 9.76)	4.41 (2.47, 7.87)	7.51 (2.1, 11.7)	3.41 (3.23, 17.5)	3.41 (2.07, 5.59)		7.40 (3.28, 16.7)	5.20 (2.04, 13.3)	3.86 (2.82, 5.70)	6.85 (3.86, 12.2)	2.90 (2.01, 4.18)		6.23 (0.80, 48.8)	7.53 (0.97, 58.3)	1.40 (0.17, 11.3)	13.1 (2.31, 76.7)	1.99 (0.60, 6.63)	
<15	4.85 (0.88, 34.6)	12.0 (5.26, 25.4)	7.19 (3.92, 13.5)	11.4 (4.97, 26.1)	4.00 (2.87, 5.56)		8.43 (2.30, 30.8)	13.6 (1.29, 104)	11.1 (4.99, 24.6)	5.72 (5.4, 23.2)	5.72 (2.98, 11.0)					13.1 (5.78, 29.7)	3.83 (1.51, 9.74)	
		1.47 (1.34, 1.62)	1.66 (1.37, 2.01)	1.98 (1.67, 2.35)				1.42 (1.32, 1.54)	1.76 (1.49, 2.09)	2.54 (1.89, 3.41)			1.74 (1.33, 2.27)	2.79 (2.15, 3.62)	3.14 (1.81, 5.42)			
ESRD																		
≥105			54.8 (4.96, 606)	47.49 (4.27, 528)	0.96 (0.19, 4.83)		3.05 (0.42, 31.3)	17.4 (2.02, 151)	27.4 (3.14, 238)	54.3 (5.56, 530)	8.64 (2.48, 30.1)		1.25 (0.38, 4.13)	1.45 (0.17, 12.6)	2.46 (0.59, 10.3)	27.9 (4.93, 158)	0.39 (0.04, 3.91)	
90-104	REF		8.33 (1.17, 59.2)				REF	3.32 (0.47, 23.7)	4.33 (1.27, 14.8)	57.2 (3.42, 959)			REF	2.56 (0.49, 13.3)	7.33 (1.32, 40.6)	26.5 (4.24, 165)		
75-89	1.76 (0.55, 5.64)		5.43 (0.71, 40.7)	72.1 (14.4, 381)	2.12 (0.83, 5.45)		1.21 (0.48, 3.10)	6.24 (2.35, 16.6)	6.55 (1.47, 29.1)	25.7 (3.81, 173.6)	1.91 (0.96, 3.80)		0.82 (0.22, 3.05)	3.80 (0.92, 15.8)	8.51 (2.52, 28.7)	50.6 (15.8, 182)	1.18 (0.55, 2.54)	
60-74	3.83 (1.23, 12.0)	24.05 (7.45, 77.6)	19.85 (5.21, 75.64)	129.52 (23.61, 710.53)	7.10 (2.97, 16.99)		3.86 (1.11, 13.4)	5.25 (0.75, 44.3)	17.38 (5.72, 52.8)	43.0 (14.4, 129)	4.41 (1.96, 8.62)		0.93 (0.30, 14.2)	5.32 (1.27, 22.4)	6.72 (1.37, 33.9)	53.6 (16.68, 172)	1.64 (0.87, 3.10)	
45-59	17.2 (5.34, 55.4)	64.5 (11.4, 366)	116 (27.5, 486)	577 (195, 1710)	27.6 (11.1, 68.7)		10.2 (3.93, 26.4)	10.5 (2.37, 46.1)	40.0 (16.1, 99.3)	155.7 (62.4, 389)	11.2 (6.01, 20.9)		3.75 (0.91, 15.5)	29.1 (6.61, 128)	25.4 (8.01, 80.8)	104 (29.2, 368)	4.05 (2.18, 7.51)	
30-44	115 (32.0, 411)	113 (8.4, 1302)	631 (96.79, 4111)	1426 (176, 11559)	93.6 (28.3, 309)		46.5 (17.3, 125)	37.6 (9.71, 146)	265 (112, 631)	512 (223, 1171)	50.8 (27.7, 93.2)		69.7 (7.19, 676)	34.9 (2.15, 566)	101 (30.8, 329)	392 (123, 1253)	12.4 (6.58, 23.4)	
15-29	625 (111, 3519)	3813 (852, 22310)	2709 (792, 9261)	8170 (1809, 35725)	526 (198, 1400)		501 (182, 1654)	296 (46.2, 1897)	725 (193, 2722)	857 (344, 2137)	116 (57.8, 232)		238 (21.2, 2662)	159 (9.80, 2575)	395 (81.8, 1905)	692 (218, 2195)	26.1 (13.3, 51.5)	
<15	20599 (4164, 100000)	48789 (8998, 269390)	37298 (7959, 180000)	1545 (423, 5644)			4132 (344, 49957)	1561 (459, 5498)	4680 (839, 26938)	375 (81.1, 1734)				2142 (253, 16145)	1439 (489, 4931)	44.3 (9.31, 211)		
		2.68 (1.32, 5.45)	7.39 (1.98, 27.6)	24.8 (7.34, 83.5)				1.30 (0.80, 2.11)	4.04 (2.75, 5.94)	10.2 (6.78, 15.5)			1.88 (0.45, 7.94)	5.55 (3.36, 9.18)	20.4 (11.9, 35.1)			

Figure 3 | Hazard ratios (HRs) of clinical outcomes according to estimated glomerular filtration rate (eGFR) and albuminuria categories across three racial groups in general population cohorts. Each number represents a pooled HRs from meta-analysis adjusted for covariates and compared with the reference cell (REF) within each race. Bold numbers indicate statistical significance at $P < 0.05$. Color shading indicates the strength of association (approximately one-quarter of all cells across racial groups are shaded in each color; green: low; yellow: mild; orange: moderate; red: high). Difference in HRs among racial groups were tested using meta-regression with Whites as a reference; *significant interaction at $P < 0.05$.

Of note, the category of eGFR 45–59 with lowest albuminuria was associated with a point estimate for the HR > 1.0 compared with the reference groups for all three outcomes for all three races (statistically significant in 7 of 9 comparisons). The category of elevated albuminuria (ACR 30–299 mg/g or urine dipstick 1+) with eGFR 90–104 was associated with a point estimate for the HR > 1.0 compared with the reference groups for all 9 comparisons (statistically significant in 8). Similar results were observed for CVD mortality and ESRD. Largely similar results were also observed across three races in both high-risk and CKD cohorts (Supplementary Figures S12 and S13 online).

DISCUSSION

Low eGFR and high albuminuria were both independently associated with an increased risk of mortality and ESRD. In this unique and large meta-analysis, we observed qualitatively similar adjusted HR for all-cause and cardiovascular mortality and ESRD according to eGFR or albuminuria across three major races, Asians, Whites, and Blacks, in general population cohorts, despite differences in demographic and clinical characteristics (Table 1) and absolute risk

(Supplementary Figure S3 online) among racial groups and cohorts. The consistency in eGFR and albuminuria risk relationships across races has important implications for clinical practice, research, and public health.

The best known racial disparities in kidney disease are the widely different ESRD rates among countries reported by the USRDS.¹⁶ Our results describing the highest ESRD rates in Blacks are consistent with other studies.^{17–20} It is more difficult to study racial differences in earlier stages of CKD. There have not been large studies of multiracial populations that have simultaneously assessed eGFR and albuminuria regarding their associations with mortality and ESRD. In addition, methods to estimate GFR and ascertain albuminuria have varied, and many studies reported only eGFR or albuminuria. Although our study has a wide variation in demographic and clinical characteristics among cohorts, the availability of both eGFR and albuminuria measurements permits a more robust analysis.

Prior reports from the CKD-PC (Chronic Kidney Disease Prognosis Consortium), using comparable methods across cohorts, showed similar impact of eGFR and albuminuria categories on relative risks of all-cause and cardiovascular

mortality and ESRD across subgroups defined by demographic and clinical characteristics (age,²¹ sex,²² hypertension,²³ and diabetes²⁴). The current analysis expands our prior observations to race groups and establishes a consistency of the relationship of eGFR and albuminuria with important outcomes irrespective of race. Given the increasing interest in variability of incidence rates of ESRD across countries and races, and the major resource implications associated with high ESRD rates, it will be important to pursue the causes for the differences in distribution of cardiovascular risk factors, eGFR, and albuminuria, which we observed among the racial groups. Specifically, it will be important to determine the extent to which social, environmental, and genetic differences result in variation in disease expression and outcomes (such as the higher prevalence of IgA nephropathy in Asia and the contribution of economic aspects to variation in dialysis care).^{25,26} A better understanding of the similarities and differences across races should direct research to identify modifiable factors.

The GFR thresholds for the definition and staging of CKD were first proposed in 2002, using data derived predominantly from a general US population.¹ In the past decade, these eGFR thresholds have been incorporated into clinical guidelines in other countries.^{3,27,28} The recognition of albuminuria as an independent risk factor for adverse outcomes has now led to the incorporation of albuminuria categories into CKD staging, and this analysis has utilized the new recommendations for categories of albuminuria and eGFR.²⁹ The robust relationship of eGFR and albuminuria with outcomes irrespective of race gives additional credence to their use in clinical arenas and beyond. Given the complexity of using race-specific thresholds of kidney measures in clinical practice, there would need to be strong evidence for justification to support their adoption.

Standardization of methods for ascertainment of GFR and albuminuria remains a challenge. Specification of race improves the accuracy of creatinine-based GFR-estimating equations by adjusting for differences in creatinine generation due to variation in muscle mass and diet. Current guidelines recommend the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation for use in North America, Europe, and Australia, which estimates GFR ~16% higher for Blacks compared with other races at a given age, gender, and level of serum creatinine.³⁰ In our study, the CKD-EPI creatinine equation demonstrates similar eGFR-risk association in Asians, Whites, and Blacks, providing further support for its usefulness across racial groups and encouraging more widespread reporting of eGFR around the world. Other equations have been developed in Japanese, Taiwanese, and Chinese, but their generalizability has not been evaluated in large studies.^{31–34} In our consortium, the selection of ACR versus dipstick for assessment of albuminuria varies across regions/cohorts and is largely based on study objectives and resources (with ACR being used most commonly in North America, Europe, and Australia, and

dipsticks being most commonly used in Asia). Therefore, we could not assess the influence of urinary creatinine *per se*, which may vary substantially across races, on the association between ACR and clinical risk.³⁵ Nevertheless, this study confirms the usefulness of both methods in relating albuminuria with outcomes, thus supporting the use of either method in clinical practice.

Strengths of our study include an international consortium with a wide range of cohorts in various settings, comprehensive data on eGFR and albuminuria, a large study population, and the assessment of both mortality and ESRD. The cohorts were not selected for previous publication regarding the study question, thereby minimizing the possibility of publication bias. The analysis was centrally coordinated, and adjustment for important variables was uniformly carried out in all cohorts. Our continuous analysis using splines allowed inspection of the pattern of association across the entire range of eGFR, irrespective of the reference point used. The categorical analysis allowed combining across cohorts that assessed albuminuria using ACR and dipstick, and provided clinically useful information.

There are several limitations in our study. Measurements of creatinine and urine albumin were not standardized in all studies, and we did not have data on measured GFR, cystatin C, or 24-h albumin excretion rate to confirm eGFR, urine ACR, or dipstick.³⁶ Only a few Asian cohorts had ACR measurements, and none of them ascertained ESRD as an outcome. Most of the Blacks in our study were from cohorts in the United States and not from the Blacks in Africa. Most Asians were in East-Asian cohorts, and we could not compare East and South Asians. Few cohorts included multiple racial groups. Further analyses will be required for Hispanics and other racial/ethnic groups not represented in this study. We cannot rule out the possibility of residual confounding due to unevaluated variables in this study, such as lifestyle (e.g., diet or physical activity) or socioeconomic status including access to health care.

Despite wide variability in clinical characteristics among cohorts and lower risk profile in Asian cohorts, there were no substantial differences among Asians, Whites, and Blacks in the independent and joint associations of reduced eGFR, based on the CKD-EPI creatinine equation, and albuminuria, based on ACR or dipstick, with all-cause and CVD mortality and ESRD. These results support the use of existing eGFR equations for risk categorization and thresholds of eGFR and albuminuria for CKD definition and staging across these racial groups.

MATERIALS AND METHODS

Study design

Details of the CKD-PC were described previously.^{8–12} To be included in the consortium, a study had to have at least 1000 participants (not applied to studies predominantly enrolling CKD patients (CKD cohorts)⁹), information at baseline on eGFR and albuminuria, and a minimum of 50 events for any of the outcomes of interest. This analysis consists of data from 45 cohorts (25 general population

cohorts, 7 high-risk cohorts with high-risk participants selected for cardiovascular or kidney disease risk factors, and 13 CKD cohorts; Table 1, Supplementary Table S2 online, and Supplementary Appendix 1 online). This study is based on secondary data analysis of pre-existing, de-identified/de-linked data set, and was approved by the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health.

Study variables

GFR was estimated using the CKD-EPI creatinine equation: $141 \times (\text{minimum of standardized serum creatinine (mg/dl)} / \kappa \text{ or } 1)^{\alpha} \times (\text{maximum of standardized serum creatinine (mg/dl)} / \kappa \text{ or } 1)^{-1.209} \times 0.993^{\text{age}} \times (1.018 \text{ if female}) \times (1.159 \text{ if Black})$, where κ is 0.7 if female and 0.9 if male, and α is -0.329 if female and -0.411 if male.^{37,38} For studies in which creatinine measurement was not standardized to isotope dilution mass spectrometry, we reduced the creatinine levels by 5%, the calibration factor used to adjust nonstandardized Modification of Diet in Renal Disease Study samples to isotope dilution mass spectrometry.³⁹ Although urine ACR is the preferred measure of albuminuria in the clinical settings,^{1,3} the semiquantitative measurement using urine dipstick in mass screening the healthy population has also been reported to be highly valuable.⁴⁰ A few studies that reported urine albumin excretion or urine protein-to-creatinine ratio were also included.¹ Race/ethnicity was categorized as Whites, Asian, Blacks, Hispanic, and others. Owing to sparse data, we could not reliably investigate Hispanics and other racial/ethnic groups (Supplementary Table S2 online), and thus their results were not shown. Diabetes mellitus was defined as fasting glucose ≥ 7.0 mmol/l, nonfasting glucose ≥ 11.1 mmol/l, hemoglobin A1c $\geq 6.5\%$, use of glucose-lowering drugs, or self-reported diabetes. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, use of antihypertensive medication, or self-reported hypertension. Hypercholesterolemia was defined as total cholesterol ≥ 5.0 mmol/l in people with prior CVD and as ≥ 6.0 mmol/l otherwise, or the use of lipid-lowering drugs. CVD history was defined as a history of myocardial infarction, coronary revascularization, heart failure, or stroke. Body mass index was calculated as weight (kg) divided by square height (m). Smoking was dichotomized as current versus former/nonsmokers. All of these study variables were assessed at baseline in every cohort.

Outcomes

The three outcomes of interest were all-cause mortality, cardiovascular mortality, and ESRD. Cardiovascular mortality was defined as death due to myocardial infarction, heart failure, sudden cardiac death, or stroke. ESRD was defined as start of renal replacement therapy or death due to kidney disease. However, death due to acute kidney injury was not included.⁴¹

Statistical analyses

Analyses were restricted to subjects aged 18 years or older. Any subject with missing values for eGFR, albuminuria, and race/ethnicity was excluded. Missing values for all other covariates were imputed by the cohort mean. Age adjustment for distribution of kidney measures and incidence rate of three outcomes was performed by direct standardization using US NHANES III as the reference population, the only cohort in the consortium representing national data by design. The analysis overview and analytic notes for individual studies are described in Supplementary Appendix 2 online.

We subsequently conducted a series of analyses stratified by racial/ethnic groups. We used a two-stage approach in which statistics were first obtained in each study and then were meta-analyzed across studies by a random-effects model. General population, high-risk, and CKD cohorts were meta-analyzed separately. Heterogeneity was quantified using the χ^2 -test for heterogeneity and the I^2 statistic. All analyses were conducted using the Stata/MP 11.2 software (www.stata.com), and a P -value < 0.05 was considered statistically significant.

Cox proportional hazards models were used to estimate the HRs of clinical outcomes associated with eGFR and albuminuria, adjusted for age, sex, history of CVD, smoking, systolic blood pressure (continuous), diabetes, serum total cholesterol concentration (continuous), body mass index (continuous), and either eGFR or albuminuria as appropriate. Death was censored for ESRD analysis. As few studies have multiple racial/ethnic groups, incorporating interaction terms between kidney measures and race in models was not practical. Therefore, meta-regression analysis with a random-effects model was used to formally compare HRs according to eGFR and albuminuria across racial/ethnic groups.⁴² We modeled eGFR and ACR using linear splines with knots at 30, 45, 60, 75, 90, and 105 ml/min per 1.73 m² (105 is not implemented for CKD cohorts) and 10, 30, and 300 mg/g (30, 300, and 1000 mg/g for CKD cohorts; to convert to mg/mmol multiply by 0.113), respectively. An eGFR of 95 ml/min per 1.73 m² (50 for CKD cohorts) and an ACR of 5 mg/g (100 for CKD cohorts) were treated as reference points.^{8,9}

We also compared the risk in categories of eGFR (< 15 , 15–29, 30–44, 45–59, 60–74, 75–89, 90–104, and ≥ 105 ml/min per 1.73 m²) and albuminuria (ACR: < 10 , 10–29, 30–299, and ≥ 300 mg/g; protein-to-creatinine ratio: < 15 , 15–49, 50–499, and ≥ 500 mg/g; dipstick: negative (–), trace (\pm), +, $\geq ++$), and their combination. For CKD cohorts, the following categories were used for eGFR (< 15 , 15–29, 30–44, 45–74, 75–89, and ≥ 90 ml/min per 1.73 m²) and albuminuria (ACR: < 30 , 30–299, 300–999, and ≥ 1000 mg/g; protein-to-creatinine ratio: < 50 , 50–499, 500–1499, and ≥ 1500 mg/g; dipstick: negative/trace, +, ++, $\geq +++$). The category with eGFR 90–104 ml/min per 1.73 m² (45–74 for CKD cohorts) and the lowest albuminuria was used as the reference group.^{8,9} Given that few Asian cohorts had ACR data, results for albuminuria were primarily shown for categories.

DISCLOSURE

All the authors declared no competing interests. All authors had full access to the analysis reports and tables and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

ACKNOWLEDGMENTS

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Carmen Peralta, Ronit Katz, Linda Fried; CIRCUS: Hiroyasu Iso, Akihiko Kitamura, Tetsuya Ohira, Kazumasa Yamagishi; COBRA: Tazeen H Jafar, Muhammad Islam, Juanita Hatcher, Neil Poulter, Nish Chaturvedi; CRIB: Martin J Landray, Jonathan Emberson, Jonathan Townend, David C Wheeler; ESTHER: Dietrich Rothenbacher, Hermann Brenner, Heiko Müller, Ben Schöttker; Framingham: Caroline S Fox, Shih-Jen Hwang, James B Meigs; Geisinger: Robert M Perkins; GLOMMS-1 Study: Nick Fluck, Laura Clark, Gordon J Prescott, Angharad Marks, Corri Black; Gubbio: Massimo Cirillo; HUNT: Stein Hallan, Knut Aasard, Cecilia M Øien, Marie Radtke; IPHS: Fujiko Irie, Hiroyasu Iso, Toshimi Sairenchi, Kazumasa Yamagishi; Kaiser Permanente NW: David H Smith, Jessica Weiss, Eric S Johnson, Micah L Thorp; KEEP: Allan J Collins, Joseph A Vassalotti, Suying Li, Shu-Cheng Chen; KP Hawaii: Brian J Lee; MASTERPLAN: Jack F. Wetzels, Peter J Blankestijn, Arjan D van Zuilen; MDRD: Mark Sarnak, Andrew S Levey, Lesley Inker, Vandana Menon; MESA: Michael Shlipak, Mark Sarnak, Carmen Peralta, Ronit Katz, Linda F Fried, Holly Kramer, Ian de Boer; MMKD: Florian Kronenberg, Barbara Kollerits, Eberhard Ritz; MRC Older People: Paul Roderick, Dorothea Nitsch, Astrid Fletcher, Christopher Bulpitt; MRFIT: Areef Ishani, James Neaton; NephroTest: Marc Froissart, Benedicte Stengel, Marie Metzger, Jean-Philippe Haymann, Pascal Houillier, Martin Flamant; NHANES III: Brad C Astor, Josef Coresh, Kunihiro Matsushita; Ohasama: Takayoshi Ohkubo, Hirohito Metoki, Masaaki Nakayama, Masahiro Kikuya, Yutaka Imai; Okinawa 83/93: Kunitoshi Iseki; Pima Indian: Robert G Nelson, William C Knowler; PREVENT: Ron T Gansevoort, Paul E de Jong, Bakhtawar Khan Mahmoodi, Stephan JL Bakker; Rancho Bernardo: Simerjot Kaur Jassal, Elizabeth Barrett-Connor, Jaclyn Bergstrom; RENAAL: Hidde J Lambers Heerspink, Barry Brenner, Dick de Zeeuw; Renal REGARDS: David G Warnock, Paul Muntner, Suzanne Judd, William McClellan; Severance: Sun Ha Jee, Heejin Kimm, Jaeseong Jo, Yejin Mok, Eunmi Choi; STENO: Peter Rossing, Hans-Henrik Parving; Sunnybrook: Navdeep Tangri, David Naimark; Taiwan GP: Chi Pang Wen, Sung-Feng Wen, Chwen-Keng Tsao, Min-Kuang Tsai, Shiuan Be Wu; ULSAM: Johan Ärnlöv, Lars Lannfelt, Anders Larsson; ZODIAC: Henk J Bilo, Hanneke Joosten, Nanne Kleefstra, Klaas H Groenier, Iefke Drion; CKD-PC Steering Committee: Brad C Astor, Josef Coresh (Chair), Ron T Gansevoort, Brenda R Hemmelgarn, Paul E de Jong, Andrew S Levey, Adeera Levin, Kunihiro Matsushita, Chi Pang Wen, Mark Woodward; CKD-PC Data Coordinating Center: Shoshana H Ballew (Coordinator), Josef Coresh (Principal investigator), Morgan Grams, Bakhtawar Khan Mahmoodi, Kunihiro Matsushita (Director), Yingying Sang (Lead programmer), Mark Woodward (Senior statistician); administrative support: Laura Camarata, Xuan Hui, Jennifer Seltzer, Heather Winegrad.

The CKD-PC Data Coordinating Center is funded in part by a program grant from the US National Kidney Foundation (NKF funding sources include Abbott) and an investigator-initiated research grant from Amgen. A variety of sources have supported enrollment and data collection, including laboratory measurements and follow-up in the collaborating cohorts of the CKD-PC. These funding sources include government agencies such as national institutes of health and medical research councils, as well as foundations and industry sponsors listed in Supplementary Appendix 3 online. The funders had no role in the design, analysis, interpretation of this study, and did not contribute to the writing of this report and the decision to submit the article for publication. The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript. A variation of this analysis was presented at the American Society of Nephrology Kidney Week 2012 (San Diego, CA, 3 November 2012).

AUTHOR CONTRIBUTIONS

Conception and design: CPW, KM, JC, BCA, RTG, ASL, and AL, CKD Prognosis Consortium. Analysis and interpretation of the data, critical revision of the article for important intellectual content, and final

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SUPPLEMENTARY MATERIAL

Appendix 1. Acronyms or abbreviations for studies included in the current report and their key references linked to the Web references.

Appendix 2. Data analysis overview and analytic notes for some of individual studies.

Appendix 3. Acknowledgments and funding for collaborating cohorts.

Table S1. Number of events per study for Asians, Whites, and Blacks.

Table S2. Characteristics of individual studies by ethnicity for Hispanics and others.

Figure S1. Crude and age-standardized distribution of eGFR and albuminuria across races in the general population cohorts. Panels A (eGFR) and B (albuminuria) show crude distribution, whereas panels C (eGFR) and D (albuminuria) are adjusted for age by direct standardization using US NHANES III as a reference population. Green, black, and red bars denote the proportions of Asian, White, and Black populations, respectively.

Figure S2. Distribution of eGFR (A and C) and albuminuria (B and D) across races in high-risk (A and B) and CKD (C and D) cohorts. Panels A (eGFR) and B (albuminuria) show high-risk cohorts, whereas panels C (eGFR) and D (albuminuria) show CKD cohorts. Green, black, and red bars denote the proportions of Asian, White, and Black populations, respectively.

Figure S3. Absolute risk overall of all-cause mortality (A and B), cardiovascular mortality (C and D), and ESRD (E and F) in general population cohorts.

Figure S4. Association of ACR by ethnicity with all-cause mortality (A) and cardiovascular mortality (B) in general population cohorts.

Figure S5. Association of eGFR by ethnicity with all-cause mortality (A) and cardiovascular mortality (B) in high-risk cohorts.

Figure S6. Association of eGFR by ethnicity with all-cause mortality (A), cardiovascular mortality (B), and ESRD (C) in CKD cohorts.

Figure S7. Association of ACR by ethnicity with all-cause mortality (A) and cardiovascular mortality (B) in high-risk cohorts.

Figure S8. Association of ACR/protein-to-creatinine ratio (PCR) by ethnicity with all-cause mortality (A), cardiovascular mortality (B), and ESRD (C) in chronic kidney disease cohorts.

Figure S9. Forest plot across general population studies by grouping of Asians, Whites, and Blacks at eGFR 45–59 category and albuminuria 30–299 category for all-cause mortality.

Figure S10. Forest plot across general population studies by grouping of Asians, Whites, and Blacks at eGFR 45–59 category and albuminuria 30–299 category for cardiovascular mortality.

Figure S11. Forest plot across general population studies by grouping of Asians, Whites, and Blacks at eGFR 45–59 category and albuminuria 30–299 category for end-stage renal disease.

Figure S12. Relative risk of all-cause and cardiovascular mortality according to eGFR and ACR/dipstick categories in Whites, Asians, and Blacks in high-risk cohorts.

Figure S13. Relative risk of all-cause and cardiovascular mortality according to eGFR and ACR/dipstick categories in Whites, Asians, and Blacks in chronic kidney disease cohorts.

Support Materials References.

Supplementary material is linked to the online version of the paper at <http://www.nature.com/ki>

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